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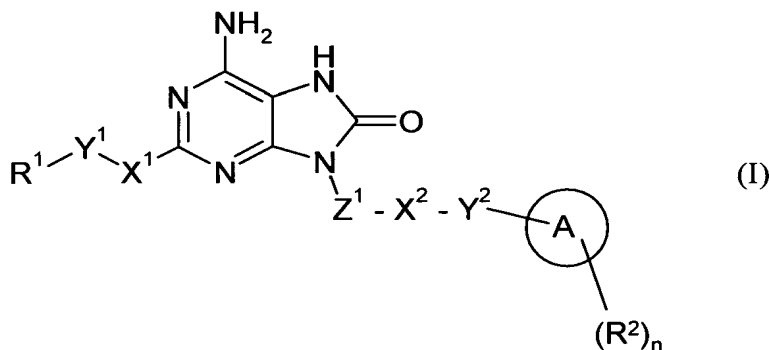
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(54) Title: 9-SUBSTITUTED-8-OXO-ADENINE COMPOUNDS AS TOLL-LIKE RECEPTOR (TLR7) MODULATORS



(57) Abstract: The present invention provides compounds of formula (I), where n, R¹, R², A, X¹, Y¹, Z¹, X² and Y² are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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9-SUBSTITUTED-8-OXO-ADENINE COMPOUNDS AS TOLL-LIKE
RECEPTOR (TLR7) MODULATORS

The present invention relates to adenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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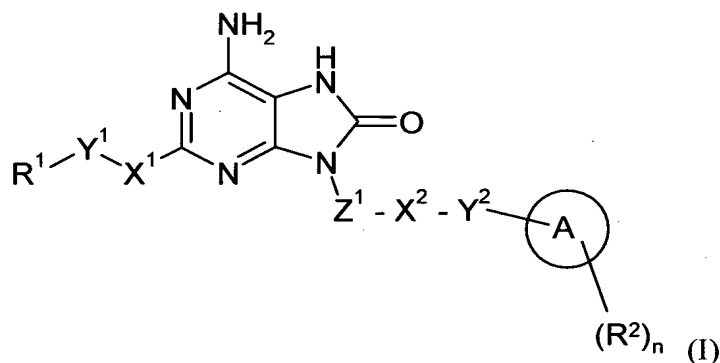
The immune system is comprised of innate and acquired immunity, both of which work cooperatively to protect the host from microbial infections. It has been shown that innate immunity can recognize conserved pathogen-associated molecular patterns through toll-like receptors (TLRs) expressed on the cell surface of immune cells. Recognition of invading
10 pathogens then triggers cytokine production (including interferon alpha(IFN α)) and upregulation of co-stimulatory molecules on phagocytes, leading to modulation of T cell function. Thus, innate immunity is closely linked to acquired immunity and can influence the development and regulation of an acquired response.

15 TLRs are a family of type I transmembrane receptors characterized by an NH₂-terminal extracellular leucine-rich repeat domain (LRR) and a COOH-terminal intracellular tail containing a conserved region called the Toll/IL-1 receptor (TIR) homology domain. The extracellular domain contains a varying number of LRR, which are thought to be involved in ligand binding. Eleven TLRs have been described to date in humans and mice. They differ
20 from each other in ligand specificities, expression patterns, and in the target genes they can induce.

Ligands which act via TLRs (also known as immune response modifiers (IRMS)) have been developed, for example, the imidazoquinoline derivatives described in US Patent No.
25 4689338 which include the product Imiquimod for treating genital warts, and the adenine derivatives described in WO 98/01448 and WO 99/28321.

This patent application describes a class of 9-substituted-8-oxoadenine compounds having immuno-modulating properties which act via TLR7 that are useful in the treatment of viral or
30 allergic diseases and cancers.

In accordance with the present invention, there is therefore provided a compound of formula



wherein

- R^1 represents hydrogen, hydroxyl, or a C_1 - C_6 alkoxy, C_2 - C_5 alkoxycarbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl or C_3 - C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_5 alkoxycarbonyl, amino (NH_2), (mono)- C_1 - C_6 alkylamino and (di)- C_1 - C_6 alkylamino;
- Y^1 represents a single bond or C_1 - C_6 alkylene;
- X^1 represents a single bond, an oxygen or sulphur atom, sulphonyl (SO_2) or NR^3 ;
- Z^1 represents a C_2 - C_6 alkylene or C_3 - C_8 cycloalkylene group, each group being optionally substituted by at least one hydroxyl;
- X^2 represents NR^4 ;
- Y^2 represents a single bond or C_1 - C_6 alkylene;
- n is an integer 0, 1 or 2;
- each R^2 group independently represents halogen, cyano, $S(O)_mR^9$, OR^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_8 cycloalkyl, the latter six groups being optionally substituted by one or more substituents independently selected from halogen, cyano, $S(O)_pR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$,

$\text{CONR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{SO}_2\text{R}^{12}$, $\text{NR}^{13}\text{CO}_2\text{R}^{12}$, $\text{NR}^{13}\text{COR}^{12}$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl and $\text{C}_3\text{-C}_8$ cycloalkyl;

R^3 represents hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^4 represents CO_2R^5 , SO_2R^5 , COR^5 , $\text{SO}_2\text{NR}^6\text{R}^7$ or CONR^6R^7 ;

5 R^5 represents

(i) a 3- to 8-membered saturated heterocyclic ring containing 1 or 2 ring heterogroups independently selected from NR^8 , S(O)_q or oxygen, the ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ alkoxy, or

10 (ii) a $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_5\text{-C}_{10}$ heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, $\text{S(O)}_t\text{R}^9$, OR^{10} , CO_2R^{10} , $\text{SO}_2\text{NR}^{10}\text{R}^{11}$, $\text{CONR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{SO}_2\text{R}^9$, $\text{NR}^{10}\text{CO}_2\text{R}^9$ and $\text{NR}^{10}\text{COR}^9$, or

(iii) a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl or $\text{C}_3\text{-C}_8$ cycloalkyl group, each of which
15 may be optionally substituted by one or more substituents independently selected from halogen, cyano, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{S(O)}_t\text{R}^{12}$, OR^{13} , COR^{13} , CO_2R^{13} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{CONR}^{13}\text{R}^{14}$, NR^6R^7 , $\text{NR}^{13}\text{SO}_2\text{R}^{12}$, $\text{NR}^{13}\text{CO}_2\text{R}^{12}$, $\text{NR}^{13}\text{COR}^{12}$, $\text{C}_6\text{-C}_{10}$ aryl and $\text{C}_5\text{-C}_{10}$ heteroaryl, the latter two substituents themselves being optionally substituted by one or more substituents independently selected from $\text{C}_1\text{-C}_6$ alkyl, halogen, hydroxy,
20 methylsulphonyl and cyano;

R^6 represents a hydrogen atom or a group selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl group and a heterocyclic moiety, which group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl,
25 OR^{15} , $\text{S(O)}_v\text{R}^{15}$, CO_2R^{16} , COR^{16} , $\text{NR}^{16}\text{R}^{17}$, $\text{CONR}^{16}\text{R}^{17}$, $\text{NR}^{16}\text{COR}^{17}$, $\text{NR}^{16}\text{CO}_2\text{R}^{15}$,

$\text{SO}_2\text{NR}^{16}\text{R}^{17}$, $\text{NR}^{16}\text{SO}_2\text{R}^{15}$, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_5\text{-C}_{10}$ heteroaryl and a heterocyclic moiety, the latter three substituents themselves being optionally substituted by one or more substituents independently selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, halogen, $\text{S(O)}_w\text{R}^{15}$, CO_2R^{16} , COR^{16} , hydroxy and cyano, and

5 R^7 represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl or $\text{C}_3\text{-C}_8$ cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_5\text{-C}_{10}$ heteroaryl, carboxy, cyano, OR^{15} , hydroxy and $\text{NR}^{18}\text{R}^{19}$, or

R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-
10 membered saturated or partially saturated heterocyclic ring optionally containing a further ring heterogroup selected from nitrogen, S(O)_x and oxygen, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{20} , $\text{NR}^{21}\text{R}^{22}$, $\text{S(O)}_y\text{R}^{23}$, COR^{24} , CO_2R^{24} , $\text{NR}^{24}\text{R}^{25}$, $\text{CONR}^{24}\text{R}^{25}$, $\text{NR}^{24}\text{COR}^{25}$, $\text{NR}^{24}\text{CO}_2\text{R}^{23}$, $\text{SO}_2\text{NR}^{24}\text{R}^{25}$, $\text{NR}^{24}\text{SO}_2\text{R}^{23}$, $\text{C}_6\text{-C}_{10}$ aryl,
15 benzyl, $\text{C}_5\text{-C}_{10}$ heteroaryl, a heterocyclic moiety, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl and $\text{C}_3\text{-C}_8$ cycloalkyl, the latter eight substituents themselves being optionally substituted by one or more substituents independently selected from halogen, oxo, cyano, OR^{21} , $\text{S(O)}_z\text{R}^{23}$, COR^{24} , CO_2R^{24} and $\text{NR}^{24}\text{R}^{25}$;

each R^8 , R^{10} , R^{11} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{24} and R^{25} independently
20 represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl group;

each R^9 , R^{12} , R^{15} and R^{23} independently represents $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;

R^{20} represents a $\text{C}_1\text{-C}_6$ alkyl group optionally substituted by one or more substituents independently selected from halogen, hydroxyl and OR^{23} ;

m, p, q, r, t, v, w, x, y and z each independently represent an integer 0, 1 or 2; and

25 A represents a $\text{C}_6\text{-C}_{10}$ aryl or $\text{C}_5\text{-C}_{12}$ heteroaryl group;

or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are effective as TLR7 agonists and may, additionally, possess properties such as low toxicity, good selectivity and/or good metabolic stability which are advantageous for pharmaceutical compounds.

In the context of the present specification, unless otherwise stated, an alkyl, alkenyl or alkynyl substituent group or an alkyl, alkenyl or alkynyl moiety in a substituent group may be linear or branched. Examples of C₁-C₆ alkyl groups/moieties include methyl, ethyl, propyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl. Examples of C₂-C₆ alkenyl and C₂-C₆ alkynyl groups/moieties include ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexadienyl, ethynyl, propynyl, 1-butyne, 2-butyne, 1-pentyne and 1-hexyne. Similarly, an alkylene group/moiety may be linear or branched. Examples of C₁-C₆ alkylene groups/moieties include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene and 1-, 2- or 3-ethylpropylene. A C₁-C₆ haloalkyl or C₁-C₆ haloalkoxy substituent group/moiety will comprise at least one halogen atom, e.g. one, two, three, four or five halogen atoms, examples of which include trifluoromethyl, trifluoromethoxy or pentafluoroethyl. The alkyl groups in a di-C₁-C₆ alkylamino group/moiety may be the same as, or different from, one another. A C₆-C₁₀ aryl or C₅-C₁₂ heteroaryl substituent group/moiety may be monocyclic or polycyclic (e.g. bicyclic or tricyclic) in which the two or more rings are fused. The heteroaryl substituent group/moiety will comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of aryl and heteroaryl groups/moieties include phenyl, 1-naphthyl, 2-naphthyl, furyl, thienyl, pyrrolyl, pyridyl, indolyl, isoindolyl, quinolyl, isoquinolyl, pyrazolyl,

imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl and oxazolyl.

A heterocyclic moiety is defined as a saturated or partially saturated 3- to 8-membered ring containing at least one ring heterogroup selected from nitrogen, S(O)_k or oxygen (where k is 0, 1 or 2), which ring may be fused with a C₆-C₁₀ aryl or C₅-C₁₂ heteroaryl group as
5 defined above. Examples of heterocyclic moieties include morpholine, azetidine, pyrrolidine, piperidine, piperazine, 3-pyrroline, isoindoline, tetrahydroquinoline and thiomorpholine. For the avoidance of doubt, it should be understood that the definitions of the heteroaryl groups and the heterocyclic moieties in formula (I) are not intended to include unstable structures or any O-O, O-S or S-S bonds and that a substituent, if present, may be attached to any suitable
10 ring atom.

When any chemical moiety or group in formula (I) is described as being optionally substituted, it will be appreciated that the moiety or group may be either unsubstituted or substituted by one or more of the specified substituents. It will be appreciated that the
15 number and nature of substituents will be selected so as to avoid sterically undesirable combinations.

In formula (I), R¹ represents hydrogen, hydroxyl, or a group selected from C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxo or n-hexoxy),
20 C₂-C₅ alkoxycarbonyl (e.g. ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl or n-pentoxycarbonyl), C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl or pentafluoroethyl), C₁-C₆, preferably C₁-C₄, haloalkoxy (e.g. trifluoromethoxy),
25 C₆-C₁₀, preferably C₆, aryl (e.g. phenyl, indenyl, naphthyl or azulenyl), C₅-C₁₀, preferably C₅-C₆, heteroaryl (e.g. pyridinyl, pyridazinyl, pyrazyl, triazinyl, indolyl, isoindolyl, quinolyl, isoquinolyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,-) and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl and oxazolyl)

and

C₃-C₈, preferably C₃-C₆, cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl),

which group may be optionally substituted by one or more (e.g. one, two, three or four)

5 substituents independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine),

hydroxyl, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, haloalkyl (e.g.

trifluoromethyl or pentafluoroethyl), C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy,

n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy),

10 C₁-C₆, preferably C₁-C₄, haloalkoxy (e.g. trifluoromethoxy),

C₂-C₅ alkoxycarbonyl (e.g. ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl,

n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl or n-pentoxycarbonyl),

amino, (mono)-C₁-C₆, preferably C₁-C₄, alkylamino (e.g. methylamino, ethylamino,

n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert-butylamino,

15 n-pentylamino or n-hexylamino) and (di)-C₁-C₆, preferably C₁-C₄, alkylamino (e.g.

dimethylamino or diethylamino).

In an embodiment of the invention, R¹ represents hydrogen, hydroxyl, or a C₁-C₄ alkoxy,

C₂-C₅ alkoxycarbonyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, phenyl, C₅-C₆ heteroaryl or

20 C₅-C₆ cycloalkyl group, each group being optionally substituted by one, two, three or four

substituents independently selected from fluorine, chlorine, hydroxyl, C₁-C₄ alkyl,

C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₂-C₅ alkoxycarbonyl, amino,

(mono)-C₁-C₄ alkylamino and (di)-C₁-C₄ alkylamino.

25 In another embodiment, R¹ represents hydrogen.

Y^1 represents a single bond or C_1-C_6 , preferably C_1-C_4 , alkylene (such as methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene or 1-, 2- or 3-ethylpropylene).

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In an embodiment of the invention, Y^1 represents C_1-C_6 alkylene.

In another embodiment, Y^1 represents C_4 alkylene, particularly n-butylene.

10 In an embodiment of the invention, X^1 represents oxygen.

In an embodiment of the invention, when X^1 represents oxygen, Y^1 represents C_1-C_6 alkylene and R^1 represents hydrogen.

15 Z^1 represents a C_2-C_6 , preferably C_2-C_4 , alkylene (e.g. ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene or 1-, 2- or 3-ethylpropylene) or C_3-C_8 cycloalkylene (e.g. cyclopropylene, cyclobutylene, cyclopentylene or cyclohexylene) group, each group being optionally substituted by at least one, e.g. one, two
20 or three, hydroxyl groups.

In an embodiment of the invention, Z^1 represents C_2-C_6 alkylene, preferably C_3 alkylene (e.g. n-propylene).

25 X^2 represents NR^4 where R^4 represents CO_2R^5 , SO_2R^5 , COR^5 , $SO_2NR^6R^7$ or $CONR^6R^7$.

In an embodiment of the invention, R^4 represents COR^5 .

Y^2 represents a single bond or C_1-C_6 , preferably C_1-C_4 , alkylene (such as methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene or 1-, 2- or 3-ethylpropylene).

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In an embodiment of the invention, Y^2 represents C_1-C_6 alkylene, particularly methylene.

R^5 represents

- (i) a 3- to 8-, preferably 5- to 6-membered saturated heterocyclic ring containing 1 or 2 ring
 10 heterogroups independently selected from NR^8 , $S(O)_q$ or oxygen, the ring being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C_1-C_6 , preferably C_1-C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and C_1-C_6 , preferably C_1-C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy,
 15 n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), or
- (ii) a C_6-C_{10} , preferably C_6 , aryl or C_5-C_{10} , preferably C_5-C_6 , heteroaryl group (examples of aryl and heteroaryl groups being the same as defined above for R^1), the aryl or heteroaryl group being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), cyano,
 20 C_1-C_6 , preferably C_1-C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_3 haloalkyl (e.g. trifluoromethyl or pentafluoroethyl), $S(O)_rR^9$, OR^{10} , CO_2R^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$ and $NR^{10}COR^9$, or
- (iii) a group selected from
 25 C_1-C_6 , preferably C_1-C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl),

C₂-C₆, preferably C₂-C₄, alkenyl (e.g. ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl or 1-hexadienyl),
 C₂-C₆, preferably C₂-C₄, alkynyl (e.g. ethynyl, propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl or 1-hexynyl) and
 5 C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl),
 which group may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or
 10 cyclohexyl), S(O)_tR¹², OR¹³, COR¹³, CO₂R¹³, SO₂NR¹³R¹⁴, CONR¹³R¹⁴, NR⁶R⁷, NR¹³SO₂R¹², NR¹³CO₂R¹², NR¹³COR¹², C₆-C₁₀, preferably C₆, aryl and C₅-C₁₀, preferably C₅-C₆, heteroaryl, the latter two substituents themselves being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 15 tert-butyl, n-pentyl or n-hexyl), halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxy, methylsulphonyl and cyano.

In an embodiment of the invention, R⁵ represents a 5- to 6-membered saturated heterocyclic ring containing 1 or 2 ring heterogroups independently selected from NR⁸, S(O)_q or oxygen,
 20 the ring being optionally substituted by one, two, three or four substituents independently selected from fluorine, chlorine, hydroxyl, C₁-C₄ alkyl and C₁-C₄ alkoxy.

In another embodiment, R⁵ represents phenyl or C₅-C₆ heteroaryl, each of which may be optionally substituted by one, two, three or four substituents independently selected from
 25 fluorine, chlorine, cyano, C₁-C₄ alkyl, trifluoromethyl, S(O)_rR⁹, OR¹⁰, CO₂R¹⁰, SO₂NR¹⁰R¹¹, CONR¹⁰R¹¹, NR¹⁰R¹¹, NR¹⁰SO₂R⁹, NR¹⁰CO₂R⁹ and NR¹⁰COR⁹.

In yet another embodiment, R^5 represents a group selected from C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl and C_3 - C_6 cycloalkyl, which group may be optionally substituted by one, two, three or four substituents independently selected from fluorine, chlorine, cyano, C_3 - C_6 cycloalkyl, $S(O)_tR^{12}$, OR^{13} , COR^{13} , CO_2R^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, NR^6R^7 ,
 5 $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, phenyl and C_5 - C_6 heteroaryl, the latter two substituents themselves being optionally substituted by one, two, three or four substituents independently selected from C_1 - C_4 , alkyl, fluorine, chlorine, hydroxy, methylsulphonyl and cyano.

10 In a still further embodiment, R^5 represents C_1 - C_4 alkyl optionally substituted by one or two substituents independently selected from fluorine, chlorine, cyano, C_3 - C_6 cycloalkyl, $S(O)_tR^{12}$, OR^{13} , COR^{13} , CO_2R^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, NR^6R^7 , $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, phenyl and C_5 - C_6 heteroaryl, the latter two substituents themselves being optionally substituted by one, two, three or four substituents independently
 15 selected from C_1 - C_4 alkyl, fluorine, chlorine, hydroxy, methylsulphonyl and cyano.

In another embodiment, R^5 represents C_1 - C_4 alkyl optionally substituted by one or two substituents independently selected from OR^{13} , CO_2R^{13} , $CONR^{13}R^{14}$, NR^6R^7 , phenyl and C_5 - C_6 heteroaryl, the latter two substituents themselves being optionally substituted by
 20 one, two, three or four substituents independently selected from C_1 - C_4 alkyl and methylsulphonyl.

In a further embodiment, R^5 represents C_1 - C_4 , preferably C_1 - C_2 , alkyl optionally substituted by one or two substituents independently selected from OR^{13} , CO_2R^{13} , $CONR^{13}R^{14}$,
 25 NR^6R^7 , phenyl and C_5 - C_6 heteroaryl (e.g. triazolyl or pyrazinyl), the latter two substituents

themselves being optionally substituted by one or two substituents independently selected from C₁-C₄ alkyl (e.g. methyl) and methylsulphonyl.

In an embodiment of the invention, R⁶ represents a hydrogen atom or a group selected from

5 C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl),

C₂-C₆, preferably C₂-C₄, alkenyl (e.g. ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl or 1-hexadienyl),

C₂-C₆, preferably C₂-C₄, alkynyl (e.g. ethynyl, propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl

10 or 1-hexynyl),

C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), and

a heterocyclic moiety,

which group may be optionally substituted by one or more (e.g. one, two, three or four)

15 substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine),

hydroxyl, oxo, cyano, C₁-C₆, preferably C₁-C₄, alkyl, C₂-C₆, preferably C₂-C₄, alkenyl, C₂-C₆, preferably C₂-C₄, alkynyl, C₃-C₈, preferably C₃-C₆, cycloalkyl, OR¹⁵, S(O)_vR¹⁵, CO₂R¹⁶, COR¹⁶, NR¹⁶R¹⁷, CONR¹⁶R¹⁷, NR¹⁶COR¹⁷, NR¹⁶CO₂R¹⁵, SO₂NR¹⁶R¹⁷, NR¹⁶SO₂R¹⁵, C₆-C₁₀, preferably C₆, aryl, C₅-C₁₀, preferably C₅-C₆, heteroaryl and a

20 heterocyclic moiety, the latter three substituents themselves being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from C₁-C₆, preferably C₁-C₄, alkyl, C₃-C₈, preferably C₃-C₆, cycloalkyl, halogen (e.g. fluorine, chlorine, bromine or iodine), S(O)_wR¹⁵, CO₂R¹⁶, COR¹⁶, hydroxy and cyano;

and

25 R⁷ represents a hydrogen atom or a C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl),

- C₂-C₆, preferably C₂-C₄, alkenyl (e.g. ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl or 1-hexadienyl),
 C₂-C₆, preferably C₂-C₄, alkynyl (e.g. ethynyl, propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl or 1-hexynyl), or C₃-C₈, preferably C₃-C₆, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group, each group being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), C₃-C₈, preferably C₃-C₆, cycloalkyl, C₆-C₁₀, preferably C₆, aryl, C₅-C₁₀, preferably C₅-C₆, heteroaryl, carboxy, cyano, OR¹⁵, hydroxy and NR¹⁸R¹⁹.
- 10 In an embodiment of the invention, R⁶ and R⁷ each represent a C₁-C₆, preferably C₁-C₄, alkyl group, e.g. methyl.

- In an alternative embodiment of the invention, R⁶ and R⁷ together with the nitrogen atom to which they are attached form a 3- to 8-, preferably 5- to 6-membered saturated or partially saturated heterocyclic ring optionally containing a further ring heterogroup selected from nitrogen, S(O)_x and oxygen, the heterocyclic ring being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, carboxyl, cyano, OR²⁰, NR²¹R²², S(O)_yR²³, COR²⁴, CO₂R²⁴, NR²⁴R²⁵, CONR²⁴R²⁵, NR²⁴COR²⁵, NR²⁴CO₂R²³, SO₂NR²⁴R²⁵, NR²⁴SO₂R²³, C₆-C₁₀, preferably C₆, aryl, benzyl, C₅-C₁₀, preferably C₅-C₆, heteroaryl, a heterocyclic moiety, C₁-C₆, preferably C₁-C₄, alkyl, C₂-C₆, preferably C₂-C₄, alkenyl, C₂-C₆, preferably C₂-C₄, alkynyl and C₃-C₈, preferably C₃-C₆, cycloalkyl, the latter eight substituents themselves being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), oxo, cyano, OR²¹, S(O)_zR²³, COR²⁴, CO₂R²⁴ and NR²⁴R²⁵.
- 25

In an embodiment of the invention, R^6 and R^7 together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring optionally containing a further ring heterogroup selected from nitrogen, $S(O)_x$ and oxygen, the heterocyclic ring being optionally substituted as defined above.

5

In another embodiment, R^6 and R^7 together with the nitrogen atom to which they are attached form a piperazinyl ring substituted by benzyl.

Each group $R^8, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{24}$ and R^{25}

10 independently represents a hydrogen atom or a C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_3 - C_6 , preferably C_5 - C_6 , cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group.

In an embodiment of the invention, each group $R^8, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19},$
15 R^{21}, R^{22}, R^{24} and R^{25} independently represents a hydrogen atom or a C_1 - C_6 , preferably C_1 - C_4 , alkyl group.

In another embodiment, each group $R^8, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22},$
 R^{24} and R^{25} independently represents a C_1 - C_4 alkyl group, particularly a methyl group.

20

Each group R^9, R^{12}, R^{15} and R^{23} independently represents C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_3 - C_6 , preferably C_5 - C_6 , cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl).

25 In an embodiment of the invention, each group R^9, R^{12}, R^{15} and R^{23} independently represents a C_1 - C_4 alkyl group, particularly a methyl group.

R^{20} represents a C_1 - C_6 , preferably C_1 - C_4 , alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl and OR^{23} .

5

A represents a C_6 - C_{10} aryl or C_5 - C_{12} , preferably C_5 - C_6 , heteroaryl group.

In an embodiment of the invention, A represents a C_6 - C_{10} aryl group, e.g. phenyl.

10 In formula (I), n is an integer 0, 1 or 2.

When n is 1 or 2, each R^2 group independently represents halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, $S(O)_mR^9$, OR^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, C_6 - C_{10} , preferably C_6 , aryl, C_5 - C_{10} , preferably C_5 - C_6 , heteroaryl, C_1 - C_6 , preferably C_1 - C_4 , alkyl, C_2 - C_6 , preferably C_2 - C_4 , alkenyl, C_2 - C_6 , preferably C_2 - C_4 , alkynyl or C_3 - C_8 , preferably C_3 - C_6 , cycloalkyl, the latter six groups being optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, $S(O)_pR^{12}$, OR^{13} , $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, C_1 - C_6 , preferably C_1 - C_4 , alkyl, C_1 - C_3 haloalkyl and C_3 - C_8 , preferably C_3 - C_6 , cycloalkyl.

20

In an embodiment of the invention, n is 0.

25 In an embodiment of the invention,

R^1 represents hydrogen;

Y^1 represents C_4 alkylene;

X^1 represents an oxygen atom;

Z^1 represents C_3 alkylene;

X^2 represents NR^4 ;

Y^2 represents methylene;

5 n is 0;

R^4 represents COR^5 ;

R^5 represents C_1 - C_2 alkyl optionally substituted by one or two substituents independently selected from OR^{13} , CO_2R^{13} , $CONR^{13}R^{14}$, NR^6R^7 , phenyl and C_5 - C_6 heteroaryl, the latter two substituents themselves being optionally substituted by one or two substituents
10 independently selected from C_1 - C_4 alkyl and methylsulphonyl;

either R^6 and R^7 both represent C_1 - C_4 alkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a piperazinyl ring substituted by benzyl;

each R^{13} and R^{14} independently represents C_1 - C_4 alkyl; and

A represents C_6 - C_{10} aryl.

15

Examples of compounds of the invention include:

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzylacetamide,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-methoxyacetamide,

20 Methyl 4-[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](benzyl)amino]-4-oxobutanoate,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-3-methoxypropanamide,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N,N'*-
25 dimethylsuccinamide,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-[4-(methylsulfonyl)phenyl]acetamide,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-(4-benzylpiperazin-1-yl)acetamide,

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-(3,5-dimethyl-1*H*-1,2,4-triazol-1-yl)acetamide,

5 *N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-3-pyrazin-2-ylpropanamide, and

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N*³,*N*³-dimethyl-β-alaninamide,

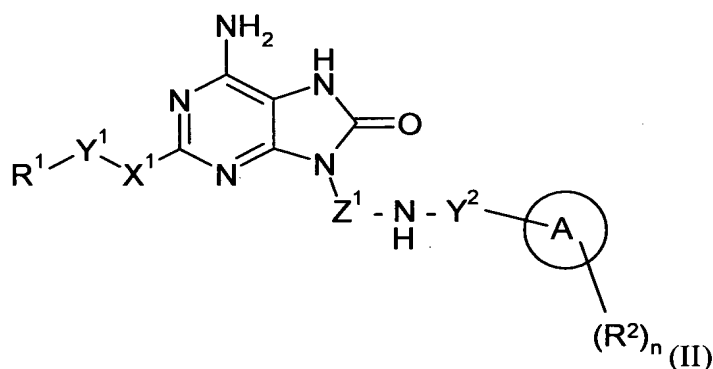
and their pharmaceutically acceptable salts.

10

It should be noted that each of the chemical compounds listed above represents a particular and independent aspect of the invention.

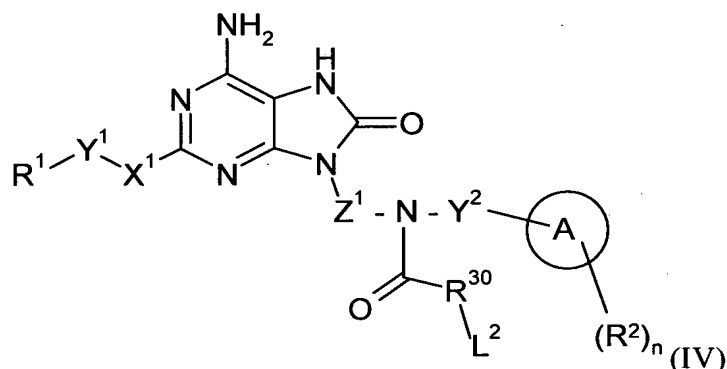
The present invention further provides a process for the preparation of a compound of formula
15 (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

(a) when R⁴ represents a group COR⁵, reacting a compound of formula



wherein n, R¹, R², A, X¹, Y¹, Z¹ and Y² are as defined in formula (I), with a compound of
20 formula (III), R⁵-C(O)-L¹, wherein L¹ represents halogen or hydroxy and R⁵ is as defined in formula (I), in the presence of a base or a coupling reagent as required;

(b) when R⁴ represents a group COR⁵ and R⁵ represents a group C₁-C₆ alkyl-NR⁶R⁷,
reacting a compound of formula



wherein R^{30} represents a C_1 - C_6 alkyl group, L^2 represents a leaving group (e.g. halogen, mesylate or triflate) and n , R^1 , R^2 , A , X^1 , Y^1 , Z^1 and Y^2 are as defined in formula (I), with a compound of formula (V), NHR^6R^7 , wherein R^6 and R^7 are as defined in formula (I), in the presence of a base;

(c) when R^4 represents a group SO_2R^5 , reacting a compound of formula (II) as defined in (a) above with a compound of formula (VI), $L^3-S(O)_2-R^5$, wherein L^3 represents a leaving group (e.g. halogen) and R^5 is as defined in formula (I), in the presence of a base;

10

(d) when R^4 represents a group CO_2R^5 , reacting a compound of formula (II) as defined in (a) above with a compound of formula (VII), $L^4-C(O)-OR^5$, wherein L^4 represents a leaving group (e.g. halogen) and R^5 is as defined in formula (I), in the presence of a base;

15 (e) when R^4 represents a group $SO_2NR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VIII), $L^5-S(O)_2-NR^6R^7$, wherein L^5 represents a leaving group (e.g. halogen) and R^6 and R^7 are as defined in formula (I), in the presence of a base;

20 or

(f) when R^4 represents a group $CONR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (IX), $L^6-C(O)-NR^6R^7$, wherein L^6 represents a leaving group (e.g. halogen) and R^6 and R^7 are as defined in formula (I), in the presence of a base;

5

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I),
- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

10

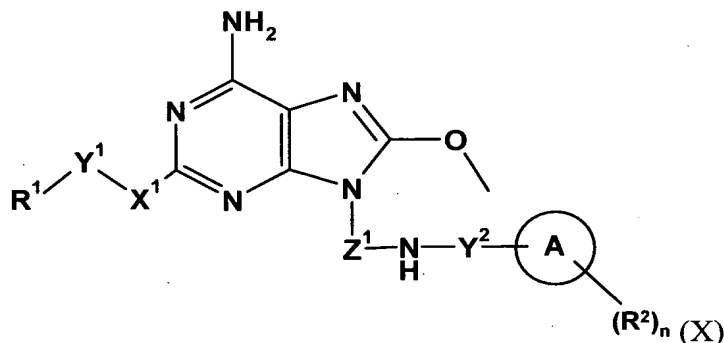
In process (a) above, the reaction is conveniently carried out in an organic solvent such as dimethylformamide, dichloromethane, acetonitrile or N-methylpyrrolidone at a temperature in the range from 0°C to 150°C. If L^1 in formula (III) represents a halogen atom, the reaction is carried out in the presence of a suitable base, examples of which include diisopropyl ethylamine, triethylamine and pyridine. If L^1 in formula (III) is hydroxy, then the reaction is carried out in the presence of a coupling reagent, suitable examples of which include benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBop), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU).

20

In process (b) above, the reaction is conveniently carried out in an organic solvent such as dimethylformamide, dimethylsulphoxide or acetonitrile at a temperature in the range from 0°C to 150°C. Suitable bases include diisopropyl ethylamine, triethylamine and pyridine.

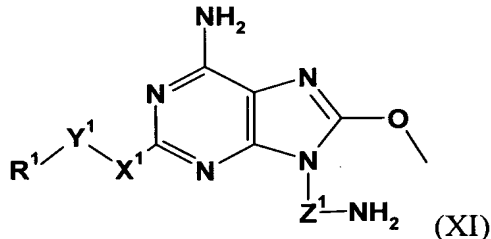
25 In each of processes (c), (d), (e) and (f) above, the reaction is conveniently carried out in an organic solvent such as dimethylformamide, dichloromethane or acetonitrile at a temperature in the range from 0°C to 150°C. Suitable bases include diisopropyl ethylamine, triethylamine and pyridine.

30 Compounds of formula (II) may be prepared by treating a compound of formula

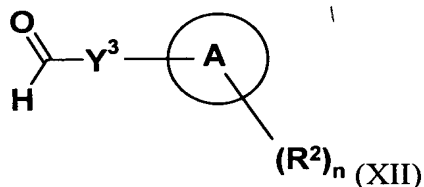


wherein n , R^1 , R^2 , A , X^1 , Y^1 , Z^1 and Y^2 are as defined in formula (II) with an acid. The reaction may be carried out in an organic solvent such as methanol, tetrahydrofuran or dioxane using either an inorganic acid such as hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as trifluoroacetic acid.

Compounds of formula (X) in which Y^2 represents C_1 - C_6 alkylene may be prepared by reacting a compound of formula

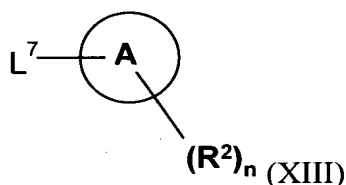


wherein R^1 , X^1 , Y^1 and Z^1 are as defined in formula (X), with a compound of formula



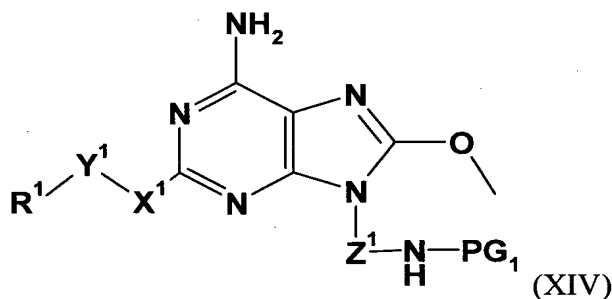
wherein Y^3 represents a bond or a C_1 - C_5 alkylene group and n , A and R^2 are as defined in formula (X). The reaction may be carried out in the presense of a suitable reducing agent (for example, sodium triacetoxyborohydride or sodium borohydride), in an organic solvent such as 1-methyl-2-pyrrolidinone, 1,2-dichloroethane, tetrahydrofuran or methanol at a temperature, for example, in the range from 0°C to 150°C .

Compounds of formula (X) in which Y^2 represents a single bond may be prepared by reacting a compound of formula (XI) as defined above with a compound of formula



wherein L^7 represents a leaving group such as halogen or mesylate and n , A and R^2 are as defined in formula (X), in the presence of a base. The reaction may be carried out in an organic solvent such as dimethylformamide, dioxane or acetonitrile at a temperature, for example, in the range from 25°C to 150°C. Suitable bases include diisopropyl ethylamine, triethylamine and potassium carbonate.

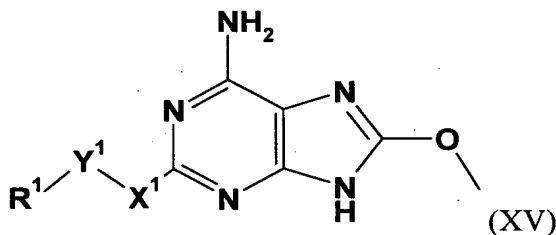
10 Compounds of formula (XI) may be prepared by treating a compound of formula



wherein PG_1 represents a protecting group (e.g. phthalimide or Fmoc) and R^1 , X^1 , Y^1 and Z^1 are as defined in formula (XI) with hydrazine in ethanol or with an organic base such as piperidine.

15

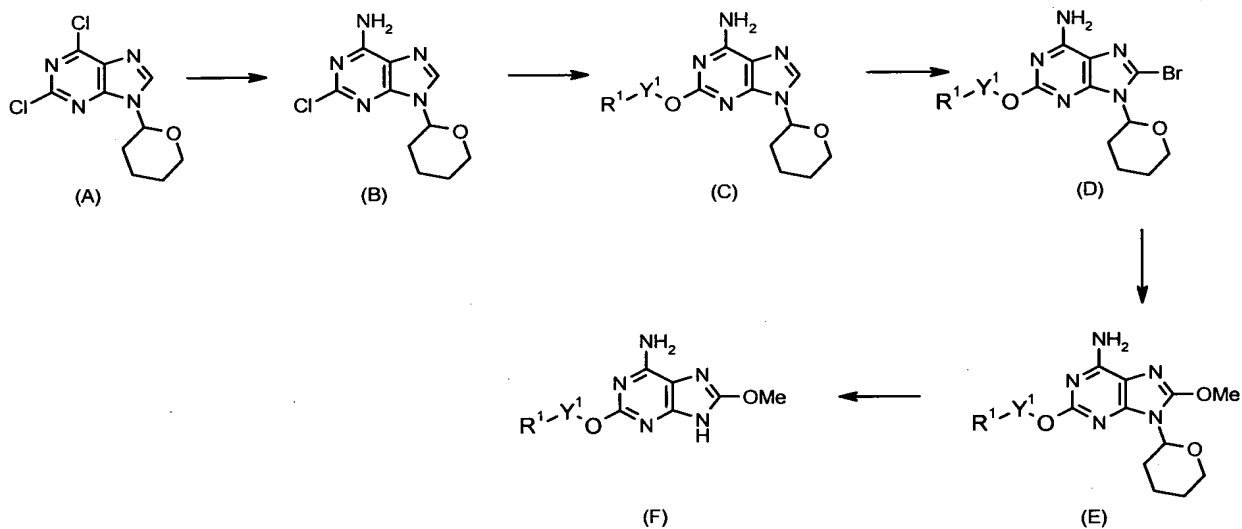
Compounds of formula (XIV) may be prepared by reacting a compound of formula



wherein R^1 , X^1 and Y^1 are as defined in formula (XIV) with a compound of formula (XVI),

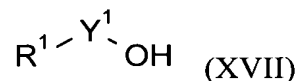
$L^8 - Z^1 - NH - PG_1$, wherein L^8 represents a leaving group (e.g. halogen, mesylate or triflate), and Z^1 and PG_1 are as defined in formula (XIV). The reaction may conveniently be carried out in an organic solvent such as dimethylformamide, dimethylsulphoxide or acetonitrile in the presense of a base such as an alkali metal carbonate (for example, sodium carbonate or potassium carbonate) or an alkaline earth metal carbonate (for example, calcium carbonate) or a metal hydroxide (for example, sodium hydroxide or potassium hydroxide), at a temperature, for example, in the range from 0°C to 150°C, preferably at room temperature (20°C).

Compounds of formula (XV) where X^1 represents an oxygen atom may be prepared as illustrated in the following reaction scheme:



The compound of formula (B) is prepared by reacting the compound of formula (A) with ammonia in an organic solvent such as methanol, ethanol, propanol, butanol, tetrahydrofuran, 1,4-dioxane, diglyme, acetonitrile or an aqueous mixture of any one of the preceding solvents. The reaction may be carried out in an autoclave and at a temperature, for example, in the range from 20°C to 200°C.

Compounds of formula (C) may be prepared by reacting the compound of formula (B) with an alcohol of formula



wherein R^1 and Y^1 are as defined in formula (XV), in the presence of a base such as sodium hydride and in an organic solvent such as tetrahydrofuran, 1,4-dioxane, diglyme, *N,N*-dimethylformamide or dimethylsulfoxide, preferably at elevated temperature, e.g. at a temperature in the range from 20°C to 150°C. Alternatively an alkali metal such as sodium may be dissolved in a C_1 - C_6 alkanol and then reacted with the compound of formula (B), preferably at elevated temperature, e.g. at a temperature in the range from 20°C to 150°C.

- Compounds of formula (D) may be prepared by brominating a compound of formula (C).
- 10 The reaction may be carried out using a brominating agent such as bromine, hydroperbromic acid or *N*-bromosuccinimide, in an organic solvent such as carbon tetrachloride, methylene chloride, dichloroethane, diethyl ether, acetic acid or carbon disulfide. The reaction temperature will generally be in the range from 0°C to the boiling point of the solvent.
- 15 Compounds of formula (E) are prepared by reacting a compound of formula (D) with sodium methoxide in an organic solvent such as methanol and at a temperature, for example, in the range from 20°C to 150°C.

Compounds of formula (F) may be obtained by treating a compound of formula (E) with an acid such as trifluoroacetic acid in an organic solvent such as methanol.

Other compounds of formula (XV) may be prepared by processes known in the art.

- Compounds of formula (IV) may be prepared by reacting a compound of formula (II) with a compound of formula (XVIII), $HO-C(O)-R^{30}-L^2$, wherein R^{30} and L^2 are as defined in formula (IV) under similar reaction conditions to those used in process (a) above.

Compounds of formulae (III), (V), (VI), (VII), (VIII), (IX), (XII), (XIII), (XVI), (XVII) and (XVIII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may
5 involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

10

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

15

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present
20 invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of toll-like receptor (especially TLR7) activity, and thus may be used in the treatment of:

- 25 1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema;
30 bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic

- infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and
- 5 chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and
- 10 delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme;
- 15 cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory
- 20 disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis;
- 25 Peyronie's disease; erectile dysfunction (both male and female);
5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel
- 30 syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease
5 and tumour recurrences, and paraneoplastic syndromes; and,
8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza;
10 bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.
- 15 Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a
20 medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

25

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those
30 who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In particular, the compounds of the invention (including pharmaceutically acceptable salts) may be used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis.

5 The invention still further provides a method of treating, or reducing the risk of, a disease or condition comprising or arising from abnormal cell growth (e.g. a cancer), which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

10

The invention also provides a method of treating, or reducing the risk of, an obstructive airways disease or condition (e.g. asthma or COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

15

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 micrograms per
20 kilogram body weight ($\mu\text{g/kg}$). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on
25 their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill
30 Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

5

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

15 The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of a sterile
20 solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); or by rectal administration in the form of suppositories.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention
25 (including pharmaceutically acceptable salts) may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 micrometres (μm), and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a
30 perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

- 5 One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard
10 gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters
15 the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato
20 starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and
25 titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain
30 granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations
5 may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention (that is, compounds of formula (I) and pharmaceutically acceptable salts thereof) may also be administered in conjunction with other compounds used
10 for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered concurrently or sequentially or as a combined preparation with
15 another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of
20 anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as
25 fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and
30 polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-ylloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;
- (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Furthermore, for the treatment of the inflammatory diseases COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as tumour necrosis factor alpha (TNF-alpha) inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin molecules (such as Enbrel); non-selective cyclo-oxygenase COX-1/COX-2 inhibitors whether applied topically

or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the invention and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention and a receptor antagonist for leukotrienes (LTB₄, LTC₄, LTD₄, and LTE₄) selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine,

chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention
5 and a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention and an antagonist of the histamine type 4 receptor.

10 The present invention still further relates to the combination of a compound of the invention and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine
15 hydrochloride.

The present invention further relates to the combination of a compound of the invention and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium
20 bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol
25 mesylate, and pirbuterol.

The present invention further relates to the combination of a compound of the invention and a chromone, such as sodium cromoglycate or nedocromil sodium.

30 The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention and a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

- 5 The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

10

- The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C
15 family) and CX3CR1 for the C-X3-C family.

- The present invention still further relates to the combination of a compound of the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or
20 inhibitors, including agents which act on cytokine signalling pathways.

- The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

25

- The present invention further relates to the combination of a compound of the invention and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

- 30 The present invention further relates to the combination of a compound of the invention together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral

agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse
 5 transcriptase inhibitor such as nevirapine or efavirenz.

The present invention will now be further explained by reference to the following illustrative examples in which the following abbreviations are used:

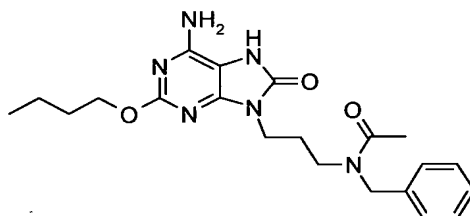
10	EtOAc	ethyl acetate
	DCM	dichloromethane
	NMP	<i>N</i> -methylpyrrolidine
	NBS	<i>N</i> -bromosuccinimide
	DMF	<i>N,N</i> -dimethylformamide
15	DMSO	dimethylsulfoxide
	THF	tetrahydrofuran
	MeOH	methanol
	TFA	trifluoroacetic acid
	HCl	hydrogen chloride
20	K ₂ CO ₃	potassium carbonate
	NaHCO ₃	sodium hydrogen carbonate
	Et ₃ N	triethylamine
	MeCN	acetonitrile
	rt	room temperature
25	h	hours
	min	minutes
	M	molar
	MS	mass spectrometry
	PyBop	Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
30	APCI	atmospheric chemical ionisation method
	ESI	electron spray ionisation method
	NMR	nuclear magnetic resonance

HCl hydrochloric acid

Unless otherwise stated organic solutions were dried over magnesium sulphate. RPHPLC denotes Reversed Phase Preparative High Performance Liquid Chromatography using Waters
5 Symmetry C8, Xterra or Phenomenex Gemini columns using acetonitrile and either aqueous ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel.

Example 1

10 ***N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzylacetamide**



(i) 2-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purin-6-amine

2,6-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purine (55g) was dissolved in 7*N*-aqueous
15 ammonia in methanol (500ml) and heated at 100°C in a sealed flask for 6h. The reaction mixture was cooled to rt and left overnight. Filtration afforded the subtitle compound.
Yield 40g.

¹H NMR δ (CDCl₃) 8.02 (1H, s), 5.94 (2H, brs), 5.71 (1H, dd), 4.15 - 4.22 (1H, m), 3.75 - 3.82 (1H, m), 1.27 - 2.12 (6H, m).

20

(ii) 2-Butoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine

The product from step (i) (40g) was dissolved in 19%(w/w)-sodium butoxide in butanol (250ml). The reaction mixture was stirred under reflux for 6h. The resultant suspension was cooled to rt, diluted with water and extracted with diethyl ether. The combined organic phase
25 was washed with water, dried and concentrated *in vacuo*. The subtitle compound was crystallized from diethyl ether/isohexane (1/1, 300ml) and obtained by filtration. Yield 19g.

¹H NMR δ (CDCl₃) 7.87 (1H, s), 5.56 - 5.68 (3H, m), 4.31 - 4.35 (2H, t), 4.14 - 4.17 (1H, m), 3.76 - 3.80 (1H, m), 1.49 - 2.08 (10H, m), 0.98 (3H, t).

(iii) 8-Bromo-2-butoxy-9-(tetrahydro-2H-pyran-2-yl) 9H-purin-6-amine

The product from step (ii) (30g) was dissolved in dry DCM (200ml). The solution was stirred at rt whilst *N*-bromosuccinimide (27g) was added portion wise. The mixture was stirred at rt
5 overnight. 20%(w/v)-Sodium sulfate (200ml) was added and the separated aqueous phase extracted with DCM. The combined organic phase was washed with saturated NaHCO₃ solution and brine. After concentration *in vacuo*, the residue was dissolved in EtOAc, washed with water, brine and dried. The solution was filtered through silica gel. The filtrate was concentrated *in vacuo* and dissolved in a mixture of diethyl ether and isohexane (1/1, 200ml)
10 to give the subtitle compound (26g). The solvent was removed to give a residue, which was purified by column chromatography (EtOAc/isohexane), which afforded 2.5g. The solids were combined to give the subtitle compound as a yellow solid. Yield 28.5g. Melting point: 148-150°C

¹H NMR δ (CDCl₃) 5.59-5.64 (3H, m), 4.32 (2H, m), 4.17 (1H, m), 3.74 (1H, m), 3.08 (1H, m), 2.13 (1H, d), 1.48 - 1.83 (8H, m), 0.98 (3H, t).
15

(iv) 2-Butoxy-8-methoxy-9-(tetrahydro-2H-pyran-2-yl) 9H-purin-6-amine

Sodium (3.7g) was added to absolute methanol (400ml) under a nitrogen atmosphere. To this solution was added the product (28.5g) from step (iii) and the mixture was stirred at 65°C for
20 9h. The mixture was concentrated *in vacuo* and 500ml of water added. The aqueous phase was extracted with EtOAc and washed with brine and dried. The subtitle compound was obtained after crystallisation from diethyl ether. Yield 14.2g.

¹H NMR δ (CDCl₃) 5.51(1H, dd), 5.28 (2H, brs), 4.29 (2H, t), 4.11 - 4.14 (4H, m), 3.70 (1H, m), 2.76 - 2.80 (1H, m), 2.05 (1H, d), 1.47 - 1.81 (8H, m), 0.97 (3H, t).
25

(v) 2-Butoxy-8-methoxy-9H-purin-6-amine, TFA salt

The product from step (iv) (24g) was dissolved in absolute methanol (300ml) and 30ml of TFA was added. The reaction mixture was stirred at rt for 3 days and concentrated *in vacuo*. The subtitle compound was obtained as a white crystalline solid after trituration with
30 methanol/EtOAc. Yield 21g.

¹H NMR δ (CD₃OD) 4.48 (2H, t), 4.15 (3H, s), 1.80 (2H, quintet), 1.50 (2H, sextet), 0.99 (3H, t).

(vi) 2-[3-(6-Amino-2-butoxy-8-methoxy-9H-purin-9-yl)propyl]-1H-isoindole-1,3(2H)-dione

The product from step (v) (15g) was dissolved in dry DMF (200ml) and 18g of K₂CO₃ added.

5 After the suspension was stirred at rt for 15min, 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione (14g) was added the the suspension vigorously stirred at rt for 10 h. The reaction mixture was extracted with EtOAc, washed with water and brine and dried. The subtitle compound was obtained after crystallisation from EtOAc/diethyl ether. Yield 16g.

¹H NMR δ (DMSO-d₆) 7.83 (4H, m), 6.73 (2H, brs), 4.06 (2H, t), 4.01 (3H, s), 3.89 (2H, t),
10 3.58 (2H, t), 2.07-2.14 (2H, m), 1.55-1.62 (2H, m), 1.31-1.40 (2H, m), 0.90 (3H, t).

(vii) 9-(3-Aminopropyl)-2-butoxy-8-methoxy-9H-purin-6-amine

The product from step (vi) (1g) was dissolved in ethanol (10ml) and hydrazine monohydrate (1ml) was added and stirred at ambient temperature for 10h. The resultant was concentrated
15 under reduced pressure and the residue suspended in DCM (10ml) and stirred for 1h. The suspension was filtered, washed with DCM. The solution was washed with water and dried. The solution was concentrated under reduced pressure to give the subtitled compound. Yield 700mg.

¹H NMR δ (DMSO-d₆) 6.77 (2H, brs), 4.16 (2H, t), 4.05 (3H, s), 3.89 (2H, t), 2.46-2.52 (2H,
20 m), 1.61-1.76 (4H, m), 1.35-1.45 (2H, m), 0.92 (3H, t).

(viii) 6-Amino-9-[3-(benzylamino)propyl]-2-butoxy-7,9-dihydro-8H-purin-8-one, dihydrochloride

The product from step (vii) (4g) and benzaldehyde (1.6g) were dissolved in THF (40ml) and
25 stirred at rt for 24h. Sodium borohydride (0.8g) and 5 drops of methanol was added and stirred at a rt overnight. The solvent was evaporated under reduced pressure and the residue partitioned between EtOAc and brine. The organic layer was separated, washed with water, dried and evaporated under reduced pressure. The residue was dissolved in MeOH (100ml), conc. HCl (10ml) added and stirred at rt for 72h. The solvent was evaporated under reduced
30 pressure and the residue triturated with MeOH/EtOAc. Yield 3.64g.

¹H NMR δ (DMSO-d₆) 10.96 (1H, s) ; 9.23 (2H, brs) ; 7.53-7.38 (5H, m) ; 4.26 (2H, t) ; 4.11 (2H, t) ; 3.78 (2H, t) ; 2.93-2.91 (2H, m) ; 2.10-2.03 (2H, m) ; 1.71-1.64 (2H, m) ; 1.46-1.36 (2H, m) ; 0.93 (3H, t)

MS: APCI (+ve): 371

5

(ix) N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl]-N-benzylacetamide

Acetylchloride (0.08ml) was added to a mixture of the product from step (viii) (250mg) and triethylamine (0.6ml) in NMP (5ml) and stirred for 2h. The mixture was purified by

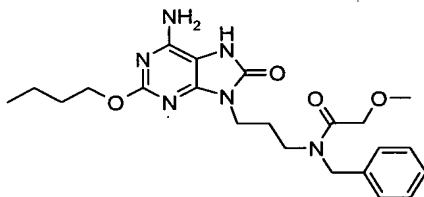
10 RPHPLC, yield 85mg.

¹H NMR δ (DMSO-d₆) rotomers present 9.86 and 9.82 (1H, 2xs) ; 7.35-7.10 (5H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.56 and 4.46 (2H, 2xs) ; 4.14-4.10 (2H, m) ; 3.68-3.60 (2H, m) ; 3.25-3.18 (2H, m) ; 2.01 and 1.99 (3H, 2xs) ; 1.95-1.80 (2H, m) ; 1.65-1.60 (2H, m) ; 1.41-1.35 (2H, m) ; 0.91 (3H, t)

15 MS: APCI (+ve): 413

Example 2

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl]-N-benzyl-2-methoxyacetamide



20

The title compound was prepared by the method of example 1 using methoxyacetyl chloride.

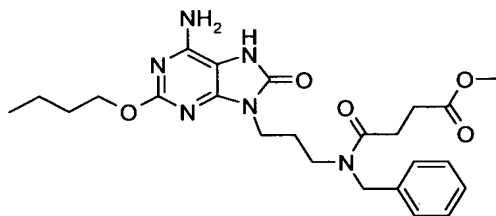
¹H NMR δ (DMSO-d₆) rotomers present 9.87 (1H, s) ; 7.34-7.11 (5H, m) ; 6.42 and 6.40 (2H, 2xs) ; 4.51 and 4.48 (2H, 2xs) ; 4.14 and 4.11 (2H, m) ; 4.07 and 4.05 (2H, 2xs) ; 3.67-3.60 (2H, m) ; 3.26-3.13 (5H, m) ; 1.96-1.81 (2H, m) ; 1.66-1.59 (2H, m) ; 1.42-1.33 (2H, m) ;

25 0.91 (3H, t)

MS: APCI (+ve): 443

Example 3

Methyl 4-[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl](benzyl)amino]-4-oxobutanoate



PyBop (0.47g) was added to a mixture of the product from example 1 step (viii) (0.25g), Et₃N (0.7ml) and succinic acid monomethyl ester (0.16g) in DMF (8ml) and stirred at rt for 4 days. MeOH (10ml) was added, the solvent evaporated under reduced pressure and the residue purified by RPHPLC, yield 46mg.

¹H NMR δ (DMSO-d₆) rotomers present 9.86 and 9.82 (1H, 2xs) ; 7.34-7.09 (5H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.60 and 4.47 (2H, 2xs) ; 4.14-4.10 (2H, m) ; 3.70-3.58 (2H, m) ; 3.57 and 3.56 (3H, 2xs) ; 3.26-3.21 (2H, m) ; 2.60-2.57 (2H, m) ; 1.98-1.78 (2H, m) ; 1.65-1.60 (2H, m) ; 1.40-1.34 (2H, m) ; 0.91 (3H, t)

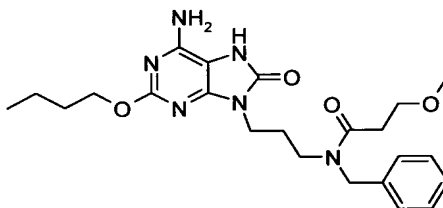
MS: APCI (+ve): 485

Examples 4-10 were prepared by the same method as Example 3.

15

Example 4

***N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl]-*N*-benzyl-3-methoxypropanamide**

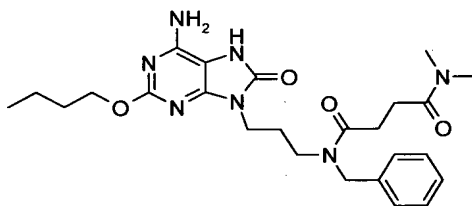


¹H NMR δ (DMSO-d₆) rotomers present 9.86 and 9.82 (1H, 2xs) ; 7.33-7.10 (5H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.58 and 4.48 (2H, 2xs) ; 4.12 (2H, t) ; 3.68-3.50 (4H, m) ; 3.25-3.23 (2H, m) ; 3.20 and 3.17 (3H, 2xs) ; 1.96-1.78 (2H, m) ; 1.67-1.58 (2H, m) ; 1.40-1.35 (2H, m) ; 0.91 (3H, t)

MS: APCI (+ve): 457

Example 5

***N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N'*,*N'*-dimethylsuccinamide**



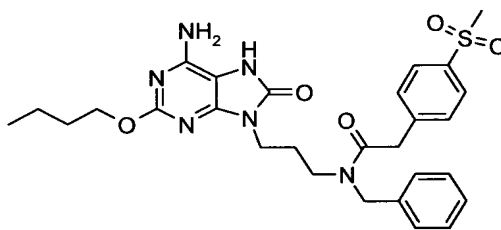
5

¹H NMR δ (DMSO- d_6) rotomers present 9.85 (1H, s) ; 7.35-7.10 (5H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.60 and 4.47 (2H, 2xs) ; 4.13-4.10 (2H, m) ; 3.69-3.60 (2H, m) ; 3.27-3.20 (2H, m) ; 2.97 and 2.95 (3H, 2xs) ; 2.80 and 2.79 (3H, 2xs) ; 2.54 (2H, s) ; 1.98-1.79 (2H, m) ; 1.64-1.59 (2H, m) ; 1.40-1.35 (2H, m) ; 0.91 (3H, t)

10 MS: APCI (+ve): 498

Example 6

***N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-[4-(methylsulfonyl)phenyl]acetamide**



15

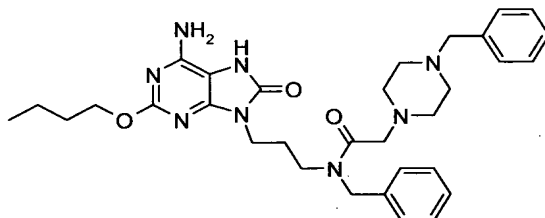
¹H NMR δ (DMSO- d_6) rotomers present 9.89 and 9.82 (1H, 2xs) ; 7.84-7.81 (2H, m) ; 7.44-7.11 (7H, m) ; 6.44-6.39 (2H, 2xs) ; 4.66 and 4.50 (2H, 2xs) ; 4.13-4.08 (2H, m) ; 3.84 (2H, s) ; 3.70-3.60 (2H, m) ; 3.29-3.26 (2H, m) ; 3.20 and 3.18 (3H, 2xs) ; 2.01-1.80 (2H, m) ; 1.66-1.56 (2H, m) ; 1.41-1.29 (2H, m) ; 0.92-0.86 (3H, m)

20 MS: APCI (+ve): 567

Example 7

***N*-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-(4-benzylpiperazin-1-yl)acetamide**

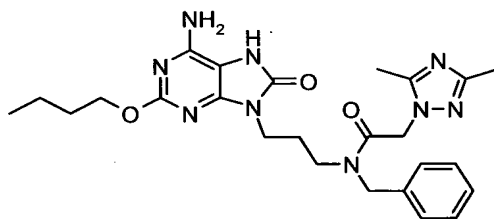
43



¹H NMR δ (DMSO- d_6) rotomers present 9.86 and 9.81 (1H, 2xs) ; 7.33-7.12 (10H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.66 and 4.48 (2H, 2xs) ; 4.15-4.09 (2H, m) ; 3.69-3.56 (2H, m) ; 3.41 and 3.35 (2H, 2xs) ; 3.32-3.14 (2H, m) ; 3.11 and 3.01 (2H, 2xs) ; 2.43-2.18 (8H, m) ; 2.02-
 5 1.75 (2H, m) ; 1.66-1.58 (2H, m) ; 1.41-1.31 (2H, m) ; 0.93-0.87 (3H, m)
 MS: APCI (+ve): 587

Example 8

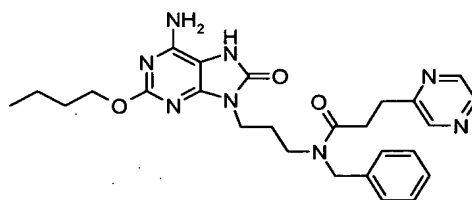
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl]-*N*-benzyl-2-(3,5-
 10 dimethyl-1H-1,2,4-triazol-1-yl)acetamide



¹H NMR δ (DMSO- d_6) rotomers present 9.86 (1H, brs) ; 7.39-7.12 (5H, m) ; 6.42 and 6.39 (2H, 2xs) ; 5.12 and 5.03 (2H, 2xs) ; 4.66 and 4.49 (2H, 2xs) ; 4.11 (2H, t) ; 3.73-3.61 (2H, m) ; 3.28-3.24 (2H, m) ; 2.24 and 2.20 (3H, 2xs) ; 2.15 and 2.12 (3H, 2xs) ; 2.06-1.80 (2H,
 15 m) ; 1.64-1.57 (2H, m) ; 1.40-1.33 (2H, m) ; 0.93-0.88 (3H, m)
 MS: APCI (+ve): 508

Example 9

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl]-*N*-benzyl-3-pyrazin-
 20 2-ylpropanamide

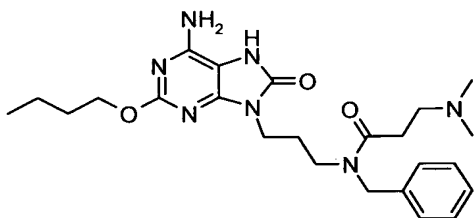


¹H NMR δ (DMSO- d_6) rotomers present 9.84 and 9.82 (1H, 2xs) ; 8.55 (1H, d) ; 8.50 (1H, d) ; 8.43 (1H, dd) ; 7.32-7.04 (5H, m) ; 6.40 (2H, s) ; 4.61 and 4.46 (2H, 2xs) ; 4.13-4.08 (2H, m) ; 3.70-3.57 (2H, m) ; 3.29-3.21 (2H, m) ; 3.04-3.00 (2H, m) ; 2.83-2.79 (2H, m) ; 1.97-1.78 (2H, m) ; 1.64-1.58 (2H, m) ; 1.38-1.34 (2H, m) ; 0.92-0.87 (3H, m)

5 MS: APCI (+ve): 505

Example 10

N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N*³,*N*³-dimethyl- β -alaninamide



10

¹H NMR δ (DMSO- d_6) rotomers present 9.87 and 9.82 (1H, 2xs) ; 7.36-7.10 (5H, m) ; 6.41 and 6.39 (2H, 2xs) ; 4.59 and 4.47 (2H, 2xs) ; 4.12 (2H, t) ; 3.69-3.60 (2H, m) ; 3.28-3.18 (2H, m) ; 2.46-2.32 (4H, m) ; 2.06-2.04 (6H, 2xs) ; 1.96-1.80 (2H, m) ; 1.65-1.59 (2H, m) ; 1.41-1.34 (2H, m) ; 0.93-0.88 (3H, m)

15 MS: APCI (+ve): 470

Biological Assay

Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably
 20 expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this
 25 reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by

determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO).

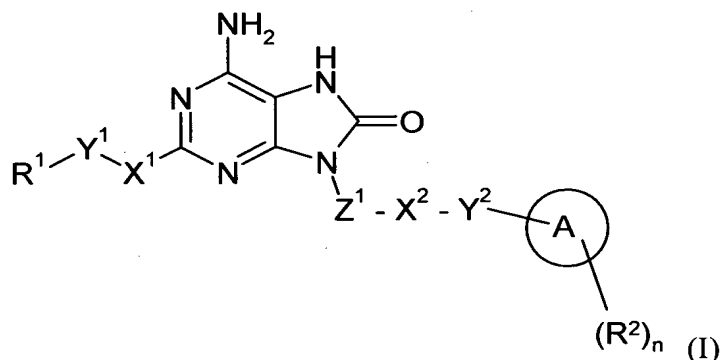
Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (pEC50). The results obtained are shown in Table 1 following.

Table 1

Compound of Example No.	pEC50
1	7.2
2	7.3
3	7.4
4	7.1
5	7.1
6	7.1
7	8.1
8	6.8
9	7.3
10	7.5

CLAIMS

1. A compound of formula



wherein

R^1 represents hydrogen, hydroxyl, or a C_1 - C_6 alkoxy, C_2 - C_5 alkoxy carbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_6 - C_{10} aryl, C_5 - C_{10} heteroaryl or C_3 - C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_5 alkoxy carbonyl, amino, (mono)- C_1 - C_6 alkylamino and (di)- C_1 - C_6 alkylamino;

Y^1 represents a single bond or C_1 - C_6 alkylene;

X^1 represents a single bond, an oxygen or sulphur atom, sulphonyl or NR^3 ;

Z^1 represents a C_2 - C_6 alkylene or C_3 - C_8 cycloalkylene group, each group being optionally substituted by at least one hydroxyl;

X^2 represents NR^4 ;

Y^2 represents a single bond or C_1 - C_6 alkylene;

n is an integer 0, 1 or 2;

each R^2 group independently represents halogen, cyano, $S(O)_mR^9$, OR^{10} , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$,

C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₈ cycloalkyl, the latter six groups being optionally substituted by one or more substituents independently selected from halogen, cyano, S(O)_pR¹², OR¹³, SO₂NR¹³R¹⁴, CONR¹³R¹⁴, NR¹³R¹⁴, NR¹³SO₂R¹², NR¹³CO₂R¹², NR¹³COR¹², C₁-C₆ alkyl,

5 C₁-C₃ haloalkyl and C₃-C₈ cycloalkyl;

R³ represents hydrogen or C₁-C₆ alkyl;

R⁴ represents CO₂R⁵, SO₂R⁵, COR⁵, SO₂NR⁶R⁷ or CONR⁶R⁷;

R⁵ represents

(i) a 3- to 8-membered saturated heterocyclic ring containing 1 or 2 ring heterogroups
 10 independently selected from NR⁸, S(O)_q or oxygen, the ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy, or

(ii) a C₆-C₁₀ aryl or C₅-C₁₀ heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C₁-C₆ alkyl,
 15 C₁-C₃ haloalkyl, S(O)_rR⁹, OR¹⁰, CO₂R¹⁰, SO₂NR¹⁰R¹¹, CONR¹⁰R¹¹, NR¹⁰R¹¹, NR¹⁰SO₂R⁹, NR¹⁰CO₂R⁹ and NR¹⁰COR⁹, or

(iii) a C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₈ cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C₃-C₈ cycloalkyl, S(O)_tR¹², OR¹³, COR¹³, CO₂R¹³, SO₂NR¹³R¹⁴,
 20 CONR¹³R¹⁴, NR⁶R⁷, NR¹³SO₂R¹², NR¹³CO₂R¹², NR¹³COR¹², C₆-C₁₀ aryl and C₅-C₁₀ heteroaryl, the latter two substituents themselves being optionally substituted by one or more substituents independently selected from C₁-C₆ alkyl, halogen, hydroxy, methylsulphonyl and cyano;

R⁶ represents a hydrogen atom or a group selected from C₁-C₆ alkyl, C₂-C₆ alkenyl,
 25 C₂-C₆ alkynyl, C₃-C₈ cycloalkyl group and a heterocyclic moiety, which group may be

optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, OR¹⁵, S(O)_vR¹⁵, CO₂R¹⁶, COR¹⁶, NR¹⁶R¹⁷, CONR¹⁶R¹⁷, NR¹⁶COR¹⁷, NR¹⁶CO₂R¹⁵, SO₂NR¹⁶R¹⁷, NR¹⁶SO₂R¹⁵, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl and a heterocyclic moiety, the latter three substituents themselves being optionally substituted by one or more substituents independently selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halogen, S(O)_wR¹⁵, CO₂R¹⁶, COR¹⁶, hydroxy and cyano, and

R⁷ represents a hydrogen atom or a C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₈ cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, carboxy, cyano, OR¹⁵, hydroxy and NR¹⁸R¹⁹, or

R⁶ and R⁷ together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated or partially saturated heterocyclic ring optionally containing a further ring heterogroup selected from nitrogen, S(O)_x and oxygen, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR²⁰, NR²¹R²², S(O)_yR²³, COR²⁴, CO₂R²⁴, NR²⁴R²⁵, CONR²⁴R²⁵, NR²⁴COR²⁵, NR²⁴CO₂R²³, SO₂NR²⁴R²⁵, NR²⁴SO₂R²³, C₆-C₁₀ aryl, benzyl, C₅-C₁₀ heteroaryl, a heterocyclic moiety, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₃-C₈ cycloalkyl, the latter eight substituents themselves being optionally substituted by one or more substituents independently selected from halogen, oxo, cyano, OR²¹, S(O)_zR²³, COR²⁴, CO₂R²⁴ and NR²⁴R²⁵;

each R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²⁴ and R²⁵ independently represents a hydrogen atom or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group;

each R⁹, R¹², R¹⁵ and R²³ independently represents C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

R^{20} represents a C_1 - C_6 alkyl group optionally substituted by one or more substituents independently selected from halogen, hydroxyl and OR^{23} ;

m, p, q, r, t, v, w, x, y and z each independently represent an integer 0, 1 or 2; and

A represents a C_6 - C_{10} aryl or C_5 - C_{12} heteroaryl group;

5 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 represents hydrogen.

3. A compound according to claim 1 or claim 2, wherein Y^1 represents C_1 - C_6 alkylene.

10

4. A compound according to any one of the preceding claims, wherein X^1 represents an oxygen atom.

5. A compound according to any one of the preceding claims, wherein Z^1 represents C_2 - C_6
15 alkylene.

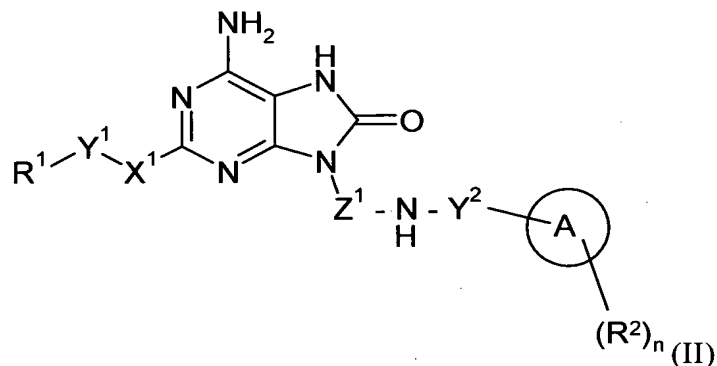
6. A compound according to any one of the preceding claims, wherein X^2 represents NR^4
and R^4 represents COR^5 .

20 7. A compound according to any one of the preceding claims, wherein R^5 represents C_1 - C_4
alkyl optionally substituted by one or two substituents independently selected from fluorine,
chlorine, cyano, C_3 - C_6 cycloalkyl, $S(O)_tR^{12}$, OR^{13} , COR^{13} , CO_2R^{13} , $SO_2NR^{13}R^{14}$,
 $CONR^{13}R^{14}$, NR^6R^7 , $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, phenyl and C_5 - C_6
heteroaryl, the latter two substituents themselves being optionally substituted by one, two,
25 three or four substituents independently selected from C_1 - C_4 alkyl, fluorine, chlorine,
hydroxy, methylsulphonyl and cyano.

8. A compound according to any one of the preceding claims, wherein Y^2 represents C_1-C_6 alkylene.
9. A compound according to any one of the preceding claims, wherein A represents C_6-C_{10} aryl.
10. A compound according to claim 1 being:
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzylacetamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-methoxyacetamide,
Methyl 4-[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](benzyl)amino]-4-oxobutanoate,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-3-methoxypropanamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N*',*N*'-dimethylsuccinamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-[4-(methylsulfonyl)phenyl]acetamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-(4-benzylpiperazin-1-yl)acetamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-2-(3,5-dimethyl-1*H*-1,2,4-triazol-1-yl)acetamide,
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-3-pyrazin-2-ylpropanamide, or
N-[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]-*N*-benzyl-*N*³,*N*³-dimethyl-β-alaninamide,
or a pharmaceutically acceptable salt of any one thereof.

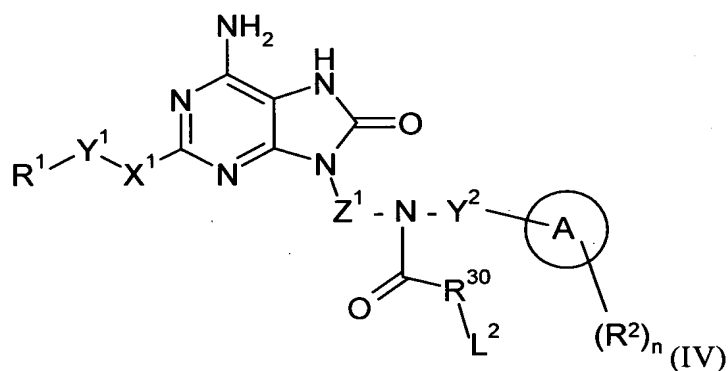
11. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1 which comprises,

(a) when R^4 represents a group COR^5 , reacting a compound of formula



wherein n , R^1 , R^2 , A , X^1 , Y^1 , Z^1 and Y^2 are as defined in formula (I), with a compound of formula (III), $R^5-C(O)-L^1$, wherein L^1 represents halogen or hydroxy and R^5 is as defined in formula (I), in the presence of a base or a coupling reagent as required;

(b) when R^4 represents a group COR^5 and R^5 represents a group C_1-C_6 alkyl- NR^6R^7 , reacting a compound of formula



wherein R^{30} represents a C_1-C_6 alkyl group, L^2 represents a leaving group and n , R^1 , R^2 , A , X^1 , Y^1 , Z^1 and Y^2 are as defined in formula (I), with a compound of formula (V), NHR^6R^7 , wherein R^6 and R^7 are as defined in formula (I), in the presence of a base;

(c) when R^4 represents a group SO_2R^5 , reacting a compound of formula (II) as defined in (a) above with a compound of formula (VI), $L^3-S(O)_2-R^5$, wherein L^3 represents a leaving group and R^5 is as defined in formula (I), in the presence of a base;

(d) when R^4 represents a group CO_2R^5 , reacting a compound of formula (II) as defined in (a) above with a compound of formula (VII), $L^4-C(O)-OR^5$, wherein L^4 represents a leaving group and R^5 is as defined in formula (I), in the presence of a base;

5

(e) when R^4 represents a group $SO_2NR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VIII), $L^5-S(O)_2-NR^6R^7$, wherein L^5 represents a leaving group and R^6 and R^7 are as defined in formula (I), in the presence of a base;

10 or

(f) when R^4 represents a group $CONR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (IX), $L^6-C(O)-NR^6R^7$, wherein L^6 represents a leaving group and R^6 and R^7 are as defined in formula (I), in the presence of a base;

15

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I),
- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

20

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25 13. A compound of formula (I) or a pharmaceutically-acceptable salt thereof as claimed in any one of claims 1 to 10 for use in the treatment of allergic or viral diseases or cancers.

14. A compound according to claim 13 which is used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.
- 5 15. A method of treating, or reducing the risk of, an allergic or viral disease or cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/000952

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/18 A61K31/522 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 728 793 A (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 6 December 2006 (2006-12-06) the whole document	1-15
P,X	WO 2008/004948 A1 (ASTRAZENECA AB, SWED.; DAINIPPON SUMITOMO PHARMA CO., LTD) 10 January 2008 (2008-01-10) examples; claims 1,15-18	1-15
P,Y	WO 2007/034916 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD., JAPAN; ASTRAZENECA AKTIEBOLAG) 29 March 2007 (2007-03-29) abstract; claims 1,15; examples 8,10 ----- -/--	1-15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 July 2008

Date of mailing of the international search report

18/07/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/000952

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2007/031726 A1 (ASTRAZENECA AB, SWED.; DAINIPPON SUMITOMO PHARMA CO. LTD.; ASTRAZENECA) 22 March 2007 (2007-03-22) examples; claims 1,14-17 -----	1-15
P,Y	WO 2007/034173 A1 (ASTRAZENECA AB, SWED.; DAINIPPON SUMITOMO PHARMA CO., LTD.; ASTRAZENECA) 29 March 2007 (2007-03-29) examples; claims 1,17-19 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/000952

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/000952

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1728793	A	06-12-2006	AU 2005226359 A1 BR PI0509258 A CA 2559036 A1 CN 1938307 A WO 2005092893 A1 KR 20070004772 A US 2007190071 A1	06-10-2005 11-09-2007 06-10-2005 28-03-2007 06-10-2005 09-01-2007 16-08-2007
WO 2008004948	A1	10-01-2008	NONE	
WO 2007034916	A1	29-03-2007	EP 1939200 A1	02-07-2008
WO 2007031726	A1	22-03-2007	AR 057131 A1 EP 1928876 A1 UY 29795 A1	14-11-2007 11-06-2008 30-04-2007
WO 2007034173	A1	29-03-2007	AR 056199 A1 EP 1928877 A1 UY 29803 A1	26-09-2007 11-06-2008 30-04-2007